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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,328	01/16/2004	Said M. Sebti	USF-T144XCZ1	8343

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EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/759,328	SEBTI, SAID M.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *6,11,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7-10 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00.

DETAILED ACTION

This office action is in response to a response to a restriction requirement filed 1/17/05. Claims 1-16 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-5, 7-10 and 12-14) in the amendment filed 1/17/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore, claims 6, 11, 15 and 16 have been withdrawn as drawn to non-elected subject matter and claims 1-5, 7-10 and 12-14 are under examination herein as much as the claims read on contacting the cell with RhoB expressed from a nucleic acid construct.

Priority

The instant application is a continuation in part of a prior filed nonprovisional application, 10/049502. Support for claims 2-4, 13 and 14 of the instant application cannot be found in the parent application. Specifically, the instant specification teaches that a cell can be contacted with RhoB in conjunction with anti-cancer agents such as TAXOL, 5'-fluoruracil and LY, which are cytotoxic and anti-signaling agents. While 10/049502 teaches methods of contacting a cell with RhoB protein in conjunction with chemotherapy, radiation therapy or therapy that selectively inhibits Ras oncogenic signaling, it does not teach addition of anti-cancer or cytotoxic or anti-signaling agents. Furthermore, 10/049,502 does not teach that RhoB can be

used to inhibit growth of cells transformed with H-Ras, N-Ras, K-Ras, EGFR and ErbB2 but not v-src as recited in the instant specification. Therefore, the effective filing date of claims 2-4, 13 and 14 is 7/21/1999.

Information Disclosure Statement

An Information Disclosure Statement filed 11/15/04 has been identified and the documents considered. The signed and initialed PTO Form 1449s has been mailed with this action.

Drawings

Figure 7B, top panel, is objected to under 37 CFR 1.83(a) because it fails to show any details as described in the specification. Specifically, figure 7B is a photograph of Western. However, the details are indiscernible as the image is too dark. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 5, 7 and 9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 of copending Application No. 10/049,502.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims. Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in 8 of copending Application No. 10/049,502. That is, the cited claims of 10/049,502 anticipate and fall entirely within the scope of the rejected claims of the instant application. Specifically, both applications recite a method of inhibiting cancer (tumor) cell growth by contacting the interior of a cell with RhoB using a nucleic acid encoding RhoB. Absent evidence to the contrary the RhoB functions to inhibit invasion, migration and metastasis, as this is inherently a part of its function.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the 10/049,502 application, then two different assignees would hold a patent to the claimed invention of 10/049,502 application, and thus improperly there would be possible harassment by multiple assignees.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-10 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants recite a genus of RhoB variant proteins.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

Applicants recite methods of inhibiting growth of a cancerous cell by contacting a cell interior with RhoB or variants thereof in which the RhoB protein or variant thereof inhibits at least one activity of the cell selected from the group consisting of migration, invasion and metastasis. Applicant teach that RhoB protein or variants thereof denotes RhoB-F, RhoB-GG and RhoB-WT proteins and variants thereof that may be derived from these proteins for example truncations, oxidations, amino acid substitutions, post-translation modifications, labeling or linkage to another molecule (page 8, line 20-24). Applicants demonstrate that administration of RhoB to a cell results in inhibition of colony formation, migration, invasion, metastasis proliferation and anoikis in a variety of cells such as A549 or NIH3T3 cells. However, applicants do not disclose the structures of these proteins or the structural regions required to provide to inhibit at least one activity of the cell selected from the group consisting of migration, invasion and metastasis. Given the diversity of RhoB variants and the inability to determine which will also possess the biologically active form, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Claims 1-5, 7-10, 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* contacting of the interior of a cell with RhoB protein to inhibit invasion or metastasis or migration does not reasonably provide enablement for *in vivo* contacting of a cell with RhoB protein or variants for the aforementioned processes. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention is directed to methods of inhibiting the growth of cancerous cells comprising contacting the cell with RhoB or variants thereof such that at least one activity of the cell is inhibited such as migration, invasion or metastasis. The invention utilizes disciplines of molecular biology, cell biology and clinical technology.

2) **Scope of the invention**. The methods of the instant invention are drawn towards methods of inhibiting cancerous growth by contacting the cell with RhoB such as by introduction of a nucleic acid encoding RhoB into a cell *in vitro* or *in vivo*. The specification specifically teaches introduction of RhoB by a viral vector. Use of the invention *in vivo* constitutes gene therapy. Steps of gene therapy exacerbate the methods of the instant invention.

3) **Number of working examples and guidance**. The specification teaches that introduction of RhoB provides a method of inhibiting the invasion, metastasis and/or migration of cancer cells transformed by an oncogene other than v-src such as H-Ras, N-Ras, K-Ras, EGFR and ErbB2. As well, the claims recite that the method further comprises administering an

additional anti-cancer agents. RhoB functions by inducing apoptosis in the cells. The methods of the instant invention are performed by introducing a nucleic acid preferably a viral vector with an event specification promoter into the cell (see e.g. page 10, paragraph 2). Applicants demonstrate that RhoB promoter activity is suppressed by H-Ras, N-Ras, K-Ras, EGFR and ErbB2 but not v-src using promoter-reporter constructs (see example 1) and furthermore that H-Ras, N-Ras and K-Ras suppress protein levels of RhoB (see example 4). However, if RhoB expression is "forced" in cells, transformation by oncogenes such as H-Ras, N-Ras, K-Ras, EGFR and ErbB2 is inhibited. This is demonstrated in NIH3T3 cells by a lack of foci formation, migration and transformation but induction of anoikis (see example 6, 8, 10, 14 and 15) and in A549 cells with an inhibition of colony formation and proliferation and induction of anoikis (see example 7, 8 and 10) and in PANC-1 cells with an inhibition of migration and invasion (see example 15, 16). As well, "forced" expression of RhoB inhibited metastasis in a mouse model. In this example, RhoB was transfected into highly metastatic melanoma cells, which were then injected into the tail vein of C57 black mice. RhoB but not pcDNA3 alone resulted in a sharp reduction in metastatic colonies (see example 19).

4) **State of Art**. The art of gene therapy is also highly unpredictable. Three major obstacles for gene therapy are 1) gene expression 2) gene delivery and 3) efficacy and toxicity of administration (Meng and El-Diery, 1999). Vector based and non-vector based means of introducing the DNA into the cell to be expressed have not successfully overcome any of these obstacles. The route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma and Somia (1997) teach, "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain

sustained expression". No modes of gene administration were proposed in the specification including means and routes of administration except to generally refer to gene expression vectors and retrovirus. To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. As noted by Marshall, (Marshall et al., Science January 17, 2003) one of the main issues in using retroviral vectors for gene therapy is determining how to use the vector in vivo without causing leukemia or other cancers in the patients being treated. This is not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled artisan can make and **use** the claimed invention for the recited treatments.

5) **Unpredictability of the art**. The unpredictable nature of administration of RhoB nucleic acid *in vivo* is exacerbated due to the lack of recited methods directed to human application. Many parameters must be addressed for *in vivo* gene delivery such as methods of delivery to avoid toxicity to normal tissues and the immune response to the delivery mechanism. Applicants have provided broad guidance for the administration of the nucleic acids. This guidance is that viral vectors are preferable. However, to date none of the proposed viral vectors overcome the three main obstacles required for gene delivery 1) gene expression 2) gene delivery and 3) efficacy and toxicity of administration. In other words, a skilled artisan cannot make the claimed invention for use in humans.

Applicants demonstrate a potential role for RhoB in multiple processes such as malignant transformation and apoptosis and even tumor growth in nude mice. However, historically *in vitro* and animal models have not correlated well with *in vivo* clinical trial results in patients. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized

nexus between the xenograft and nude mice experimental models and the human disease state. "Although animal studies have suggested low toxicity and excellent efficacy, these investigation have been limited by the use of immuno-deficient mice" (Meng and Deiry, p. 6, column 1). The success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies. Many *in vitro* and animal models that are provided as evidence of success of treatment have not translated into successful treatment in humans.

Summary. The invention recites methods of inhibiting the growth of cancerous cells comprising contacting the cell with RhoB or variants thereof such that at least one activity of the cell is inhibited such as migration, invasion or metastasis. The unpredictability of using the claimed invention in therapy is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbates a highly unpredictable art.

In view of the unpredictability of the art to which the invention pertains and the lack of guidance in the specification: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5, 7-9 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by et al Du et al (MCB, March 1999, Vol 19,No 3, pages 1831-1840; see entire document).

This rejection is based upon a reading of the claims based upon administration of RhoB *in vitro* to cells. As stated above in the 112, first paragraph rejection, "the success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies". Hence this rejection cannot be considered to provide an enabling disclosure for *in vivo* therapy as recited in the instant application.

Du et al teach a method of inhibiting cell growth of transformed cells, which inherently means that invasion, migration and metastasis are all inhibited in these cells, by introduction of a plasmid expressing RhoB. The cells were assayed for colony formation, anchorage independent and dependent growth and cell growth, which are an explicit measure of metastasis and migration inhibition *in vitro* (see e.g. page 1833, col 2, paragraph 2) as recited in claim 1 and 5. As regards claims 2 and 3, RhoB was introduced into the cells in combination with farnesyltransferase inhibitors, which Du et al teach are antitumor agents that function to inhibit signal transduction as evidenced by Prendergast et al. Du et al teach that RhoB mediates transcriptional activation of p21wafl by the FTI, which sensitizes the cell to the FTI (see page

1836, col 2, paragraph 1) as recited in claim 4. The cells are derived from Rat/ras transformed cells lines expressing H-ras. The Rat1 fibroblasts form solid tumors *in vivo* as recited in claims 9, 13 and 14 and are transfected *in vitro*. The cells are transfected in an aqueous solution, which is a pharmaceutically acceptable carrier (see e.g. page 1832, col 2, paragraph 1). Furthermore, the mixture comprises calcium phosphate, which targets the plasmid to the cell surface for entry and hence can be considered a targeting molecule in the absence of a definition in the specification as to this term.

Claims 1, 5, 7, 9 and 12 are rejected under 35 U.S.C. 102(a) and claims 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Du and Prendergast (Cancer Research, Vol 59, pages 5492-5496, November 1999; see entire document).

This rejection is based upon a reading of the claims based upon administration of RhoB *in vitro* to cells. As stated above in the 112, first paragraph rejection, "the success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results inpatients and have not translated into successful human therapies". Hence this rejection cannot be considered to provide an enabling disclosure for *in vivo* therapy as recited in the instant application.

Du et al teach a method of inhibiting cell growth of transformed cells, which inherently means that invasion, migration and metastasis are all inhibited in these cells, by introduction of a plasmid expressing RhoB. The cells were assayed for colony formation, anchorage independent and dependent growth and cell growth, which are an explicit measure of metastasis and migration inhibition *in vitro* (see e.g. figure 1 and page 5494, col 1, paragraph 1) as recited in

claim 1, 5 and 12. Several cell lines are subjected to treatment with plasmids expressing RhoB such as MCF7 MDA-MB-231, both of which are Ras transformed and form solid tumors *in vivo* as recited in claims 9, 13 and 14. Regarding claims 7 and 8, the cells are transfected in an aqueous solution, which is a pharmaceutically acceptable carrier (see e.g. page 5493, col 1, paragraph 1). Furthermore, the mixture comprises lipofectamine, which targets the plasmid to the cell surface for entry and hence can be considered a targeting molecule in the absence of a definition in the specification as to this term.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

August 5, 2004

Daniel M. Sullivan
Patent Examiner